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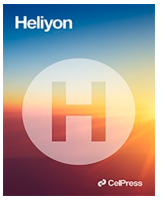

Review article

The role of Cyclin Dependent Kinase Inhibitor 3 (*CDKN3*) in promoting human tumors: Literature review and pan-cancer analysis

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ABSTRACT

Background: Although many experiments and clinical studies have proved the link between the expression of *CDKN3* and human tumors, we have not been able to identify any bioinformatics study in which the extensive tumor-promoting effect of *CDKN3* was systematically analyzed.
Objective: Explore the extensive tumor-promoting effects of *CDKN3* and review the research progress of *CDKN3* in cancer.
Methods: We systematically reviewed the literature on *CDKN3* and tumors. We explored the potential tumor-promoting effects of *CDKN3* on different tumors in the TCGA database and the GTEx database using multiple platforms and websites. We studied the expression level of *CDKN3*, survival, prognosis, diagnosis, genetic variation, immune infiltration, and enrichment analysis using databases such as TIMER 2.0, GEPIA2, cBioPortal, and STRING.
Results: We found that *CDKN3* is highly expressed in most tumors. The expression of *CDKN3* is closely related to the prognosis of some tumors. And *CDKN3* may have diagnostic value. The conclusion of our literature review is roughly the same, but there are differences, which are worthy of further study. Moreover, *CDKN3* may be related to immune cell infiltration in tumor tissues. The genetic alteration of LUAD, STAD, SARC, PCPG, and ESCA with "Amplification" as the main type. In addition, through enrichment analysis, we found that *CDKN3* affects tumors mainly through the control of the cell cycle and mitosis.
Conclusion: CDKN3 is highly expressed in most tumor tissues and has a statistical correlation with survival prognosis. It has extensive tumor-promoting effects that may be related to mechanisms such as immune infiltration.

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1. Introduction

The rising incidence and mortality of tumors have become a burden all over the world, so looking for markers with broad cancer-promoting effects is still necessary [1–5]. Cyclin dependent kinase inhibitor 3 (*CDKN3*), is a cell cycle regulator [6]. In 1994, Hannon and colleagues used a yeast two-hybrid system to study proteins interacting with *CDK2* and discovered a protein in HeLa cells named *CDK*-associated phosphatase (*KAP*) because of its binding to *CDK* [7]. *CDKN3* is a phosphatase that can dephosphorylate serine/threonine and has been located at chromosome 14q22 through FISH technique in 1995 [8,9]. It has a molecular weight of 23kD and can be alternately activated in different cell cycles, phosphorylating the corresponding substrates to orderly advance the cell cycle. It is reported that Thr-161 and Thr-160 are the activation sites of *CDK* phosphorylation [10,11]. *CDKN3* can dephosphorylate Thr-161/Thr-160, thereby inhibiting the progress of the cell cycle [12]. Moreover, as an interacting protein of murine double minute 2 (*Mdm2*), CDKN3 can form a complex with *Mdm2* and *p53*, which may inhibit the activation of *p21*, reduce the expression of *p53*, and promote DNA replication and cell proliferation [13,14].

Increasingly studies have found that *CDKN3* plays a variety of roles in tumors, such as cell cycle regulation, tumor invasion, and metastasis [15–17]. However, due to the emergence of *CDKN3* mutants, although *CDKN3* is highly expressed in some tumors, it is still a tumor suppressor gene [18]. Cress et al. found that the expression level of *CDKN3* is not constant in the cell cycle, and its peak occurs during mitosis [11]. The study of Chen et al. has shown that *CDKN3* can affect the prognosis of hepatocellular carcinoma [19]. As a factor regulating the cell cycle, *CDKN3* can open up a new way for tumor therapy by determining its role in different tumors. The current research results show that the mechanism of *CDKN3* involves many aspects, such as cell cycle, apoptosis, invasion, migration, and mutants, but it still can not explain why it plays different roles in tumors. The pan-correlation of *CDKN3* with tumors is still poorly understood.

Through a systematic review of the literature, we summarized the characteristics of the experimental research and bioinformatic analysis on *CDKN3*. The Cancer Genome Atlas (TCGA) database (https://portal.gdc.cancer.gov/) and the Genotype Tissue Expression (GTEx) database (https://www.genome.gov/Funded-Programs-Projects/Genotype-Tissue-Expression-Project) include functional genomic data sets of various tumors [20–22], which can be used for high-throughput genome analysis. Therefore, there is a reliable data source for pan-cancer analysis of *CDKN3* through bioinformatics technology [23]. We found that the expression of *CDKN3* in tumors is controversial, but generally presents a role in promoting tumor progression. According to the literature review, the correlation between *CDKN3* and tumors is complemented by pan-cancer analysis. However, some differences warrant a more in-depth study.

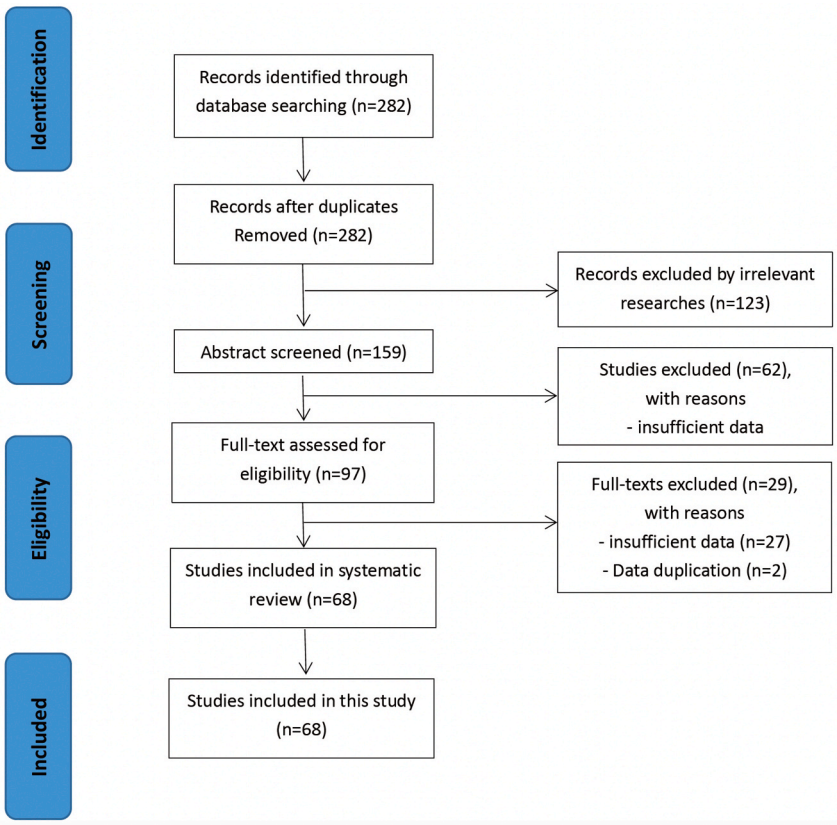

Fig. 1. Flow diagram of selection of *CDKN3* and tumor studies.

2. Materials and methods

2.1. Data acquisition and gene expression analysis

We searched PubMed (https://pubmed.ncbi.nlm.nih.gov/) for studies that met the criteria by December 2023. The search terms were set to "Cyclin dependent kinase inhibitor 3" OR "*CDKN3*" OR "*KAP*" AND "tumors*" OR "Neoplasms*" OR "cancers*". The study we include must be about the impact of *CDKN3* on the prognosis of tumor patients. The study must include the comparison of *CDKN3* expression in tumor and normal tissues. However, if it is a pharmacological study on the treatment of tumors with *CDKN3* or a study by indirectly calculating the changes of *CDKN3* expression, whether there is a direct experiment or bioinformatics analysis, it will be excluded by us. For those studies, his research data can not be used, such as data duplication and high data similarity, and we will not include them. In addition, if a set of data is published multiple times, the newly published study is included, only once [24]. The selection process is to be briefed by complying with the PRISMA flow diagram (Fig. 1) [25].

We obtained the difference in *CDKN3* expression between tumor tissues and normal tissues in TCGA in the "Gene_DE" column of the Tumor Immune Estimation Resource, version 2 (TIMER 2.0) (https://cistrome.shinyapps.io/timer/) [26–28]. However, there was an absence of corresponding normal tissues for ACC, DLBC, HNSC, LAML, LGG, MESO, OV, SARC, SKCM, TGCT, THYM, UCS, and UVM. Therefore, we also applied the "Expression Analysis-Box Plot" the module of the Gene Expression Profiling Interactive Analysis, version 2 (GEPIA2) (http://gepia2.cancer-pku.cn) [29]. We reset the parameters as follows: "*P*-value Cutoff = 0.01, logFC (log2 fold change) Cutoff = 1" and "Match TCGA normal and GTEx data". Then the box plots of *CDKN3* expression difference between these tumor tissues and corresponding normal tissues from GTEx database were obtained. We also set "log2 [TPM(Transcripts per million)+1] for log-scale" in another module "Stage Plot" to obtain the expression of *CDKN3* in all TCGA tumors at different pathological stages (I-IV), which is presented with box or violin plots [30].

2.2. Survival prognosis and diagnosis analysis

The overall survival (OS) and disease-free survival (DFS) can evaluate the survival of tumors. Significance map data of *CDKN3* in all TCGA tumors were obtained by using the "Survival Map" module of GEPIA2. The threshold of the high-expression and low-expression cohort is divided by a high cut-off value (50%) and a low cut-off value (50%) [27]. We obtained the survival map through the item "survival analysis" in GEPIA2, using the log-rank test as the hypothesis test. We also analyzed the survival data on the Kaplan-Meier Plotter (https://kmplot.com/analysis/) [31]. The data used was also downloaded from TCGA. The analyses and plotting of the receiver operating characteristic (ROC) curves were implemented by R software (version 4.1.2), timeROC (version 0.4), and ggplot2 (version 3.3.3).

2.3. Genetic alteration analysis

We searched the genetic alteration characteristics of *CDKN3* on the cBioPortal database (https://www.cbioportal.org/) [32,33]. We observed some results in the "Cancer Types Summary" module. The alteration frequency, mutation type, and copy number alteration (CNA) across all TCGA tumors were included. The mutation site information of *CDKN3* was represented by using the "Mutations" module. We used the corresponding protein structure map or 3D structure to present [27].

2.4. Immune infiltration analysis

We used the "Immune-Gene" module of the TIMER 2.0 to explore the association between *CDKN3* expression and immune infiltrates. Cancer-associated fibroblasts (CAFs), regulatory T cells (Tregs), and T cell follicular helper (TFH) were selected as immune cells. We applied EPIC, MCP-COUNTER, CIBERSORT, CIBERSORT-ABS, and QUANTISEQ algorithms to estimate immune infiltration. The *P*-value and partial correlation (cor) values were obtained via the purity-adjusted Spearman's rank correlation test [34,35]. And we visualized the data as a heatmap and a scatter plot.

2.5. CDKN3-related gene enrichment analysis

We first searched the STRING database (http://string-db.org/) with "*CDKN3*" as the only protein name and "Homo Sapiens" as the only organism [36,37]. Then, we changed the parameters: selecting "experiments" only in "active interaction sources", using "Low confidence (0.150)" as the minimum required interaction score, selecting "no more than 50 interactors" in the first line, and "none" in the second line as the max number of interactors to show [38]. Finally, the available, experimentally determined *CDKN3* binding protein was obtained.

Then we obtained the first 100 targeted genes related to *CDKN3* based on data sets by using the "Similar Gene Detection" module of GEPIA2. In addition, the "Gene_Corr" module of TIMER 2.0 provided heat map data of selected genes [39]. The Kyoto Encyclopedia of Genes and Genomes (KEGG) and Gene Ontology (GO) path analysis were performed and accomplished [40–42].

Then, the top 10 pathways of KEGG were selected using qvalueFilter (corrected *P*-value filter condition) = 0.05, making the results more statistically significant. The top 10 items of biological process (BP), cellular component (CC), and molecular function (MF) in GO with qvalueFilter same settings as KEGG [43,44].

Table 1
The significance of *CDKN3* in tumors was revealed by the literature review.

Author	Year	Cancer type	Expression of *CDKN3*	Effect on cancer	Sample	Study type
Xiao et al. [45]	2018	adrenocortical carcinoma	up	P	GEO	E + B
Xu et al. [46]	2019	adrenocortical carcinoma	up	P	GEO	B
Guo et al. [47]	2020	adrenocortical carcinoma	up	P	GEO	B
Li et al. [48]	2022	bladder cancer	up	P	TCGA; CL	E + B
Deng et al. [49]	2016	breast cancer	up	P	CL	E
Qi et al. [50]	2019	breast cancer	up	P	GEO	B
Shinden et al. [51]	2021	breast cancer	up	P	people sample; CL	E
Lee et al. [52]	2000	breast and prostate cancer	up	P	CL	E
Cekanova et al. [53]	2008	colorectal cancer	up	P	CL	E + B
Yang et al. [54]	2015	colorectal cancer	up	P	CL	E
Li et al. [55]	2020	colorectal cancer	up	P	people sample; CL	E
Su et al. [56]	2016	esophageal carcinoma	up	P	GEO	E + B
Wang et al. [57]	2019	esophageal cancer	up	P	people sample; TCGA; GEO	E + B
Liu et al. [58]	2019	esophageal squamous cell carcinoma	up	P	people sample; CL	E
Yu et al. [59]	2020	esophageal squamous cell carcinoma	up	P	CL	E
Wang et al. [60]	2021	esophageal squamous cell carcinoma	up	P	GEO	B
Li et al. [61]	2017	gastric cancer	up	P	people sample; CL	E
Liu et al. [62]	2018	gastric cancer	up	P	GEO	B
Maués et al. [63]	2020	gastric adenocarcinoma	down	P	people sample; CL; GEO	E
Abdel-Tawab et al. [64]	2022	gastric cancer	up	P	people sample	E
Li et al. [65]	2015	glioblastoma	down	P	CL	E
Yu et al. [18]	2007	glioblastoma	down	P	people sample; CL	E
Xing et al. [66]	2012	hepatocellular carcinoma	up	P	CL	E
Lin et al. [67]	2013	hepatocellular carcinoma	up	P	people sample; CL	E
Dai et al. [68]	2016	hepatocellular carcinoma	down	P	CL	E
Zhou et al. [69]	2018	hepatocellular carcinoma	up	P	GEO	B
Sang et al. [70]	2018	hepatocellular carcinoma	up	P	GEO	B
Zhang et al. [71]	2018	hepatocellular carcinoma	up	P	GEO	B
Zhou et al. [72]	2019	hepatocellular carcinoma	up	P	GEO	B
Wu et al. [73]	2019	hepatocellular carcinoma	up	P	GEO	B
Ma et al. [74]	2019	hepatocellular carcinoma	up	P	GEO	B
Wu et al. [75]	2019	hepatocellular carcinoma	up	P	GEO	B
Dai et al. [17]	2020	hepatocellular carcinoma	up	P	CL; GEO	B
Xu et al. [76]	2020	hepatocellular carcinoma	up	P	GEO	B
Wang et al. [77]	2021	hepatocellular carcinoma	up	P	TCGA; GEO	B
Wang et al. [78]	2021	hepatocellular carcinoma	up	P	GEO	B
Zhang et al. [79]	2021	hepatocellular carcinoma	up	P	GEO; TCGA; ICGC	B
Dai et al. [80]	2021	hepatocellular carcinoma	up	P	GEO	B
Chen et al. [19]	2020	hepatocellular carcinoma	up	P	GEO	B
Zhan et al. [81]	2021	hepatocellular carcinoma	up	P	GEO	B
Kim et al. [82]	2022	hepatocellular carcinoma	up	P	GEO	B
Wu et al. [83]	2022	hepatocellular carcinoma	up	P	TCGA	E + B
Fan et al. [84]	2015	lung adenocarcinoma	up	P	people sample; CL	E
Ni et al. [85]	2019	lung adenocarcinoma	up	P	GEO	B
Wang et al. [86]	2021	lung adenocarcinoma	up	P	GEO	B
Liu et al. [87]	2022	lung cancer	up	P	people sample; GEO	E + B
Tang et al. [88]	2013	non-small cell lung cancer	up	P	people sample	E
Gao et al. [16]	2019	non-small-cell lung cancer	down	P	CL	E
Tu et al. [89]	2019	non-small cell lung cancer	up	P	GEO	B
Wang et al. [90]	2017	nasopharyngeal carcinoma	up	P	people sample	E
Chang et al. [91]	2018	nasopharyngeal carcinoma	up	P	people sample	E
Barrón et al. [92]	2015	cervical cancer	up	P	people sample	E
Gao et al. [93]	2023	endometrial cancer	up	P	GTEx; TCGA; people sample	E + B
Li et al. [94]	2014	epithelial ovarian cancer	up	P	people sample	E
Zhang et al. [95]	2015	ovarian cancer	up	P	CL	E
Liu et al. [96]	2018	pancreatic ductal adenocarcinoma	up	P	CL	E
Yu et al. [97]	2017	prostate cancer	up	P	CL	E
Gu et al. [98]	2021	prostate cancer	up	P	GEO	B
Wang et al. [99]	2021	prostate cancer	up	P	GEO	B
Chen et al. [100]	2021	prostate cancer	up	P	GEO	B
Lai et al. [101]	2012	renal cancer	up	P	people sample	E
Wei et al. [102]	2019	clear cell renal cell carcinoma	up	P	TCGA	B

(*continued on next page*)

Table 1 (*continued*)

Author	Year	Cancer type	Expression of *CDKN3*	Effect on cancer	Sample	Study type
Sharie et al. [103]	2023	clear cell renal cell carcinoma	up	P	TCGA	B
Laczmanska et al. [104]	2020	renal cell carcinoma	up	P	GEO	B
Cen et al. [15]	2021	renal cell carcinoma	down	P	people sample; CL	E + B
Li et al. [105]	2018	thyroid cancer	up	P	people sample; mouse; CL	E
Chen et al. [13]	2014	chronic myelogenous leukemia	up	I	CL	E
Zhang et al. [106]	2022	testicular cancer	up	P	GEO	B

Abbreviations: *P* promote; *I* inhibit; *GEO* Gene Expression Omnibus database; *TCGA* the Cancer Genome Atlas; *CL* cell line; *ICGC* International Cancer Genome Consortium; *E* experiment; *B* bioinformatics analysis.
Note: "up" represents the upregulation of *CDKN3* expression; "down" represents the downregulation of *CDKN3* expression. "P" represents that *CDKN3* presents a tumor-promoting effect; "I" represents that *CDKN3* exhibits tumor development inhibitory effects. "E" stands for the type of study is experimentally validated; "B" stands for the type of study is bioinformatics analysis.

3. Results

3.1. The significance of CDKN3 revealed by literature review

After excluding the literature that did not meet the criteria, we included 68 studies. Then we summarized and extracted the key contents in Table 1. It is not difficult to see from Table 1 that the expression of *CDKN3* in 18 major types of tumors shows different trends. But in general, it is up-regulated in most tumors. The tumor types include adrenocortical carcinoma, bladder cancer, breast cancer, colorectal cancer, cervical cancer, esophageal cancer, gastric cancer, glioblastoma, hepatocellular carcinoma, lung adenocarcinoma, non-small cell lung cancer, nasopharyngeal carcinoma, ovarian cancer, prostate cancer, pancreatic ductal adenocarcinoma, thyroid cancer, renal cancer, testicular cancer, and others. In these tumors, the high expression of *CDKN3* plays a role in promoting tumor development except in chronic myelogenous leukemia. Interestingly, the down-regulated expression of *CDKN3* in gastric adenocarcinoma, glioblastoma, hepatocellular carcinoma, non-small cell lung cancer, and renal cell carcinoma also promotes tumor development (Table 1).

3.2. Gene expression analysis

We used the TIMER 2.0 website to analyze the expression of *CDKN3* in various tumor-type TCGA websites. The expression of *CDKN3* is higher in BLCA, BRCA, CHOL, COAD, ESCA, GBM, HNSC, KICH, KIRC, KIRP, LIHC, LUAD, LUSC, PRAD, STAD, UCEC (all $P < 0.001$), CESC, PCPG, READ, THCA (all $P < 0.01$) and PAAD ($P < 0.05$) (Fig. 2A).

For the cancer types without corresponding normal tissues that were not available in TCGA, we used the normal tissues of the GTEx dataset on the GEPIA2 website as a control. We found a difference in terms of *CDKN3* expression between normal and cancer tissues for ACC, BRCA, DLBC, HNSC, LAML, OV, SARC, SKCM, TGCT, THYM, and UCS (all $P < 0.05$, Fig. 2B).

We observed a correlation between *CDKN3* and the pathological stage of cancer for ACC, BRCA, KICH, KIRC, LIHC, LUAD, LUSC, and OV by using the "Pathological Stage Plot" module of GEPIA2 (all $P < 0.05$, Fig. 2C).

3.3. Survival analysis data

The tumor patients were divided into two groups according to the expression level of *CDKN3* to explore the prognostic value of *CDKN3* expression in patients with different tumors. This is based on the TCGA dataset. We found that the high expression of *CDKN3* is associated with the poor OS of 8 kinds of tumors. The Kaplan–Meier curves of 6 kinds of tumors are shown in Fig. 3A. These eight kinds of tumors are ACC, KIRC, KIRP, LGG, LUAD, MESO, PAAD, and UVM (all $P < 0.05$). However, we found that the high expression of the *CDKN3* gene is correlated with the good OS in THYM ($P < 0.05$). In addition, the DFS analysis revealed that, in TCGA cases, high expression of *CDKN3* was correlated with poor DFS for patients with ACC, ESCA, KIRC, KIRP, LGG, LIHC, LUAD, MESO, PAAD, PRAD, SARC, and UVM (all $P < 0.05$). The Kaplan–Meier curves of 6 kinds of tumors are shown in Fig. 3B. What is strange is that in STAD, the high expression of *CDKN3* is a protective factor for patients in the prognostic analysis of DFS.

To evaluate the prognostic value of *CDKN3* in the 9 types of cancers where *CDKN3* was significantly associated with poor OS, time-dependent prognostic ROC curves were plotted. The area under the curve (AUC) of the prognostic signature for 1-year OS, 3-year OS, and 5-year OS of ACC, KIRC, KIRP, LGG, LUAD, MESO, PAAD, and UVM was over 0.6, 6 kinds of tumors are shown in Fig. 3C. It indicated that *CDKN3* is an acceptable prognostic factor.

3.4. Genetic alteration analysis data

We observed the genetic alteration status of *CDKN3* on the cBioPortal website. We found that the "Amplification" of *CDKN3* is the main type of genetic alteration. The change frequency of *CDKN3* in patients with DLBC was the highest (>2%). Tumors dominated by the "Amplification" as the genetic alteration type include LUAD, STAD, SARC, PCPG, and ESCA. The CNA "Mutation" type is the main

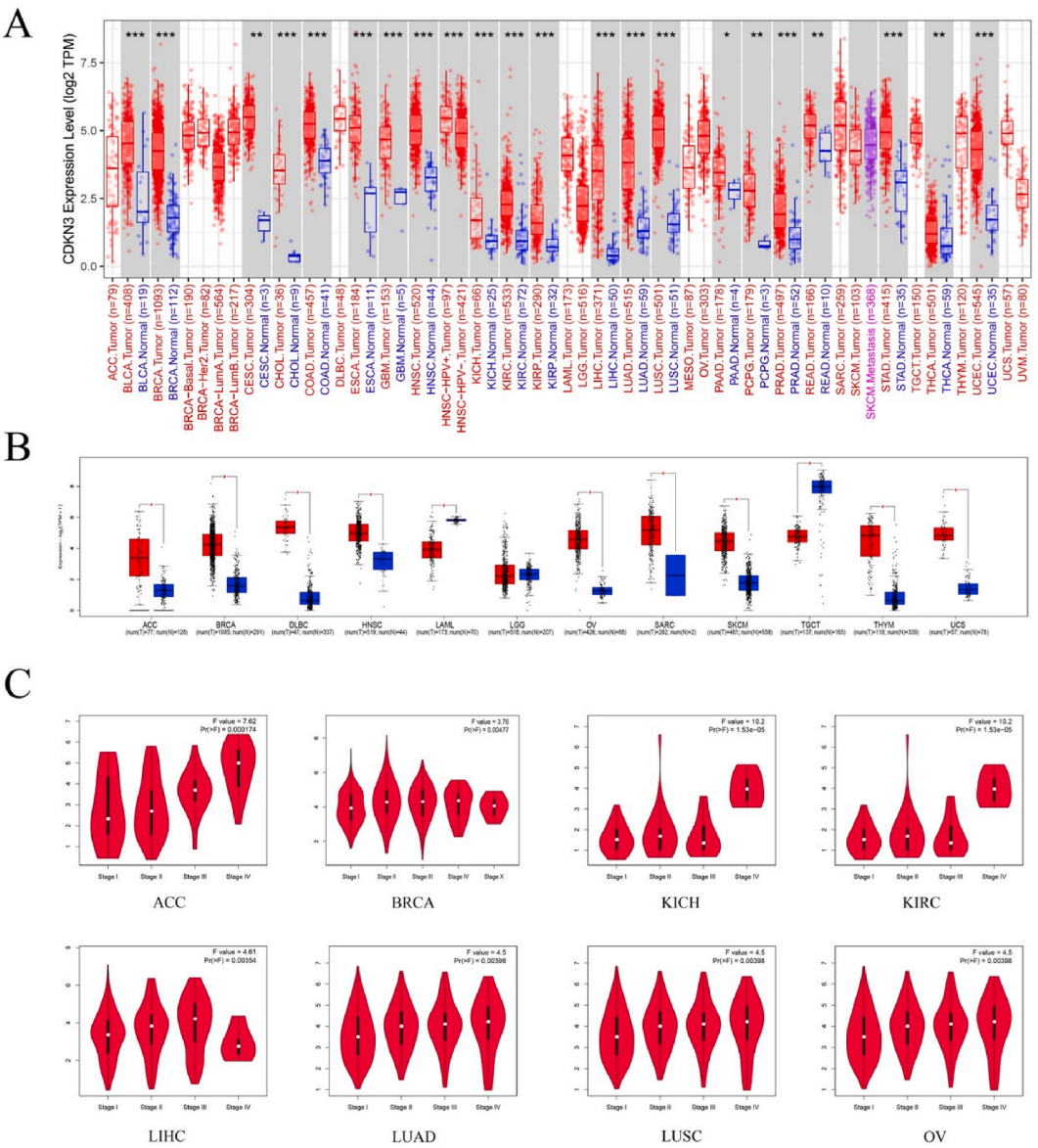

Fig. 2. Expression levels of *CDKN3* in diverse cancers. **(A)** The expression of *CDKN3* in various cancer types from the Gene_DE module of the TIMER2 website. **(B)** The expression level of *CDKN3* in different tumors was analyzed by the TIMER2 website. **(C)** A correlation between *CDKN3* expression and the pathological stage of some cancers was analyzed by GEPIA2. (*p < 0.05; **p < 0.01; ***p < 0.001; ns, not significant.)

genetic alteration type for UCEC, TGCT, KIRC, and BLCA cases. It shows a change frequency of about 1.32% in UCEC. Moreover, all MESO cases with genetic changes (about 1.15% frequency) have *CDKN3* copy number deletion (Fig. 4A). The types, sites, and case numbers of *CDKN3* gene changes are further shown in Fig. 4B. The R (arginine) is translated to Q (glutamine) at position 193 (R193Q) changes detected in 2 cases of UCEC can induce a shift mutation of *CDKN3*. And the position in the 3D structure of the *CDKN3* protein can be observed in Fig. 4C.

3.5. Immune infiltration analysis data

We observed that the expression of *CDKN3* was statistically positively correlated with the infiltration value of tumor-associated fibroblasts (TAFs) in ESCA, KICH, KIRC, KIRP, and THCA (all $P < 0.05$) (Fig. 5A). The results showed that *CDKN3* was statistically positively correlated with the infiltration levels of TFH in BRCA, GBM, KIRP, LIHC, STAD, THCA, THYM, and UVM (all $P < 0.05$) (Fig. 5B). The results of the TIMER 2.0 database revealed that *CDKN3* was positively correlated with the infiltration levels of Tregs in KIRC, LIHC, and THCA (all $P < 0.05$) (Fig. 5C).

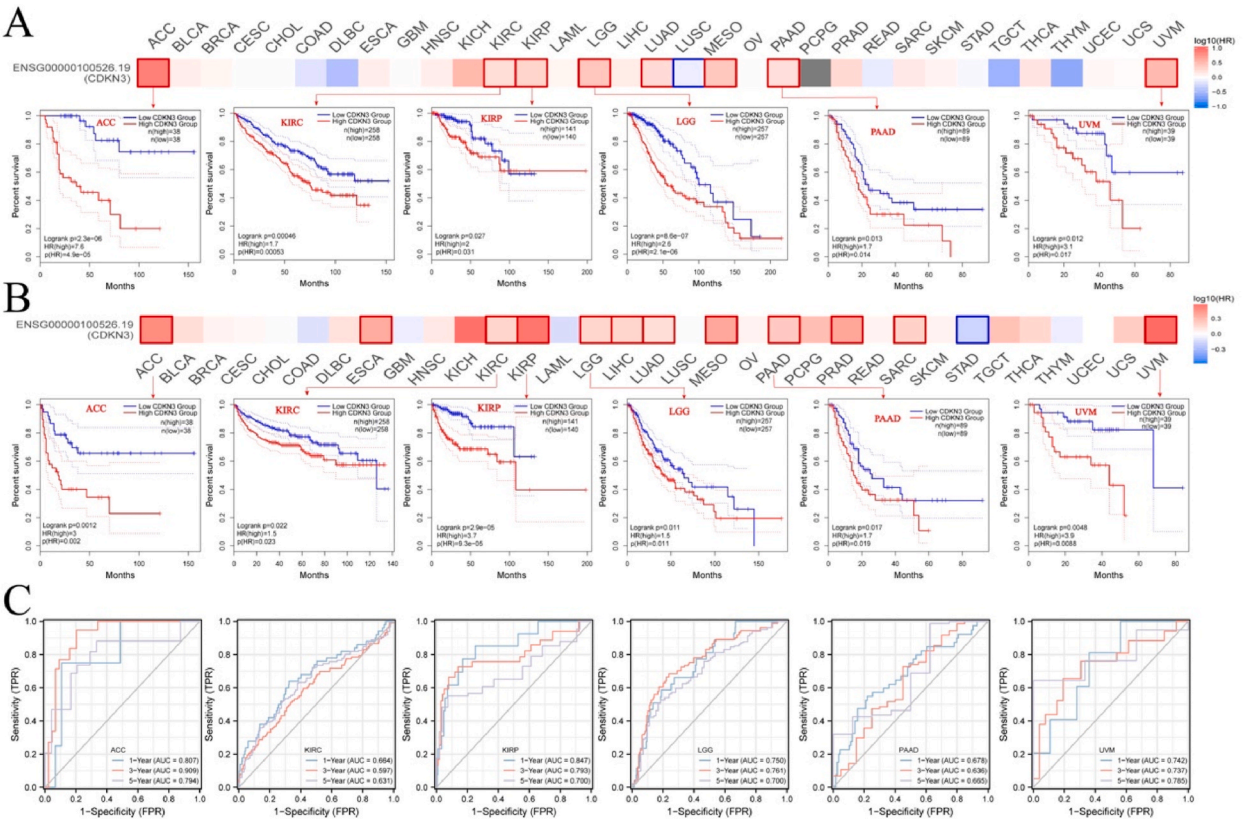

Fig. 3. Kaplan–Meier analysis and time independent receiver operating characteristic (ROC) curves of *CDKN3* in different cancer types. **(A)** Overall survival (OS) of different cancers. **(B)** Disease-free survival (DFS) of different cancers. **(C)** The ROC curves of *CDKN3* in different cancer types.

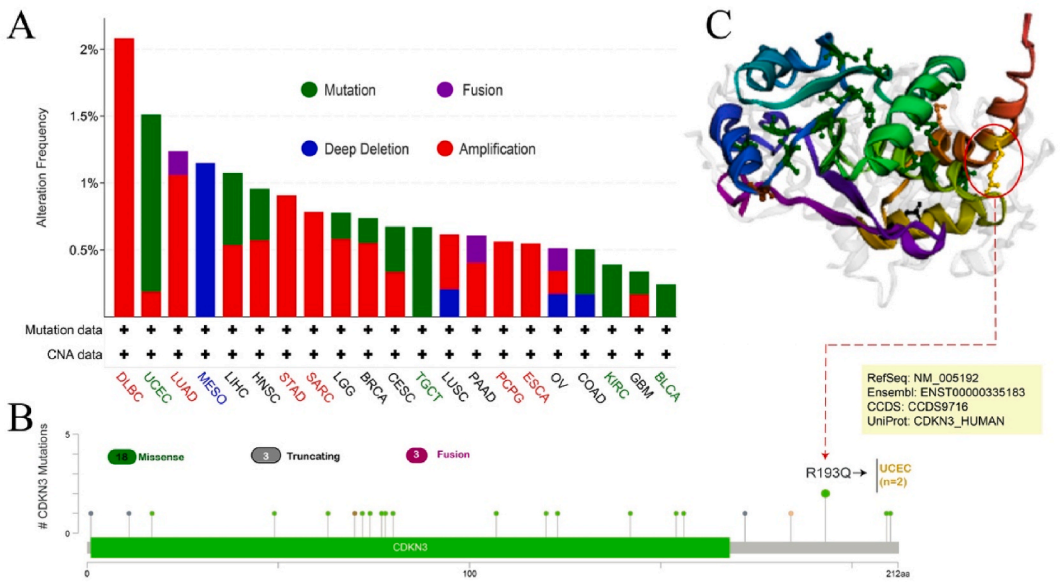

Fig. 4. The genetic alteration status of *CDKN3* on the cBioPortal website. **(A)** Frequency of the mutation type. **(B)** Mutation site. **(C)** The position in the 3D structure of the *CDKN3* protein.

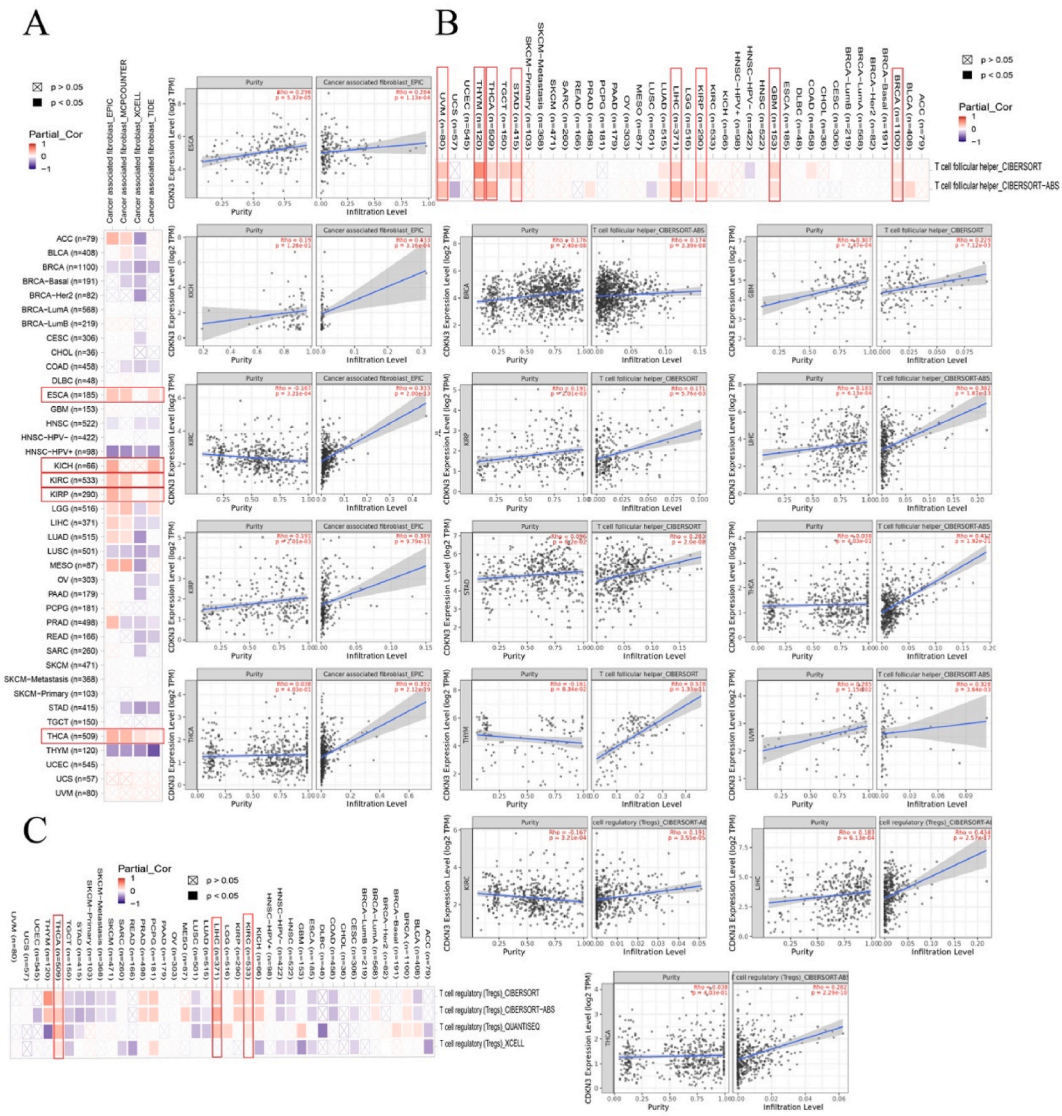

Fig. 5. *CDKN3* expression and immune infiltration: correlation analysis. **(A)** cancer-associated fibroblasts (CAF). **(B)** T cell follicular helper (TFH). **(C)** regulatory T cells (Tregs).

3.6. Enrichment analysis of CDKN3

Through the STRING database, we obtained a network diagram of 50 *CDKN3* binding protein interactions (Fig. 6A). We used the GEPIA2 tool to combine all tumor expression data from TCGA and obtained the top 100 genes related to *CDKN3* expression. The expression of *CDKN3* was positively correlated with the expression levels of non-SMC condensin II complex subunit G2 (R = 0.78), nucleolar and spindle associated protein 1 (R = 0.78), lamin B1 (R = 0.77), kinesin family member 15 (R = 0.75), minichromosome maintenance complex component 6 (R = 0.74) and DNA methyltransferase 1 (R = 0.68) genes (all P < 0.01). The corresponding heatmap also showed a positive correlation between *CDKN3* and the above 5 genes (FAM104A, TTLL5, TUBG1, WDR53, WDR62) in tumors (Fig. 6B).

We performed KEGG and GO enrichment analyses of these two gene sets. KEGG data suggest that *CDKN3* may play a role in tumors through a variety of signal pathways. It may be related to signal pathways such as "Cell cycle", "DNA replication", "MicroRNAs in cancer", "cellular senescence", and "viral carcinogenesis" (Fig. 6C). The enrichment analysis of GO revealed that these genes are related to cytokinesis, division pathways, or biogenesis, as shown in Fig. 6D, mainly acting on cellular process and dephosphorylation in the BP group, acting on the spindle and chromosomal region in the CC group, and mainly acting on protein serine kinase activity in the MF group.

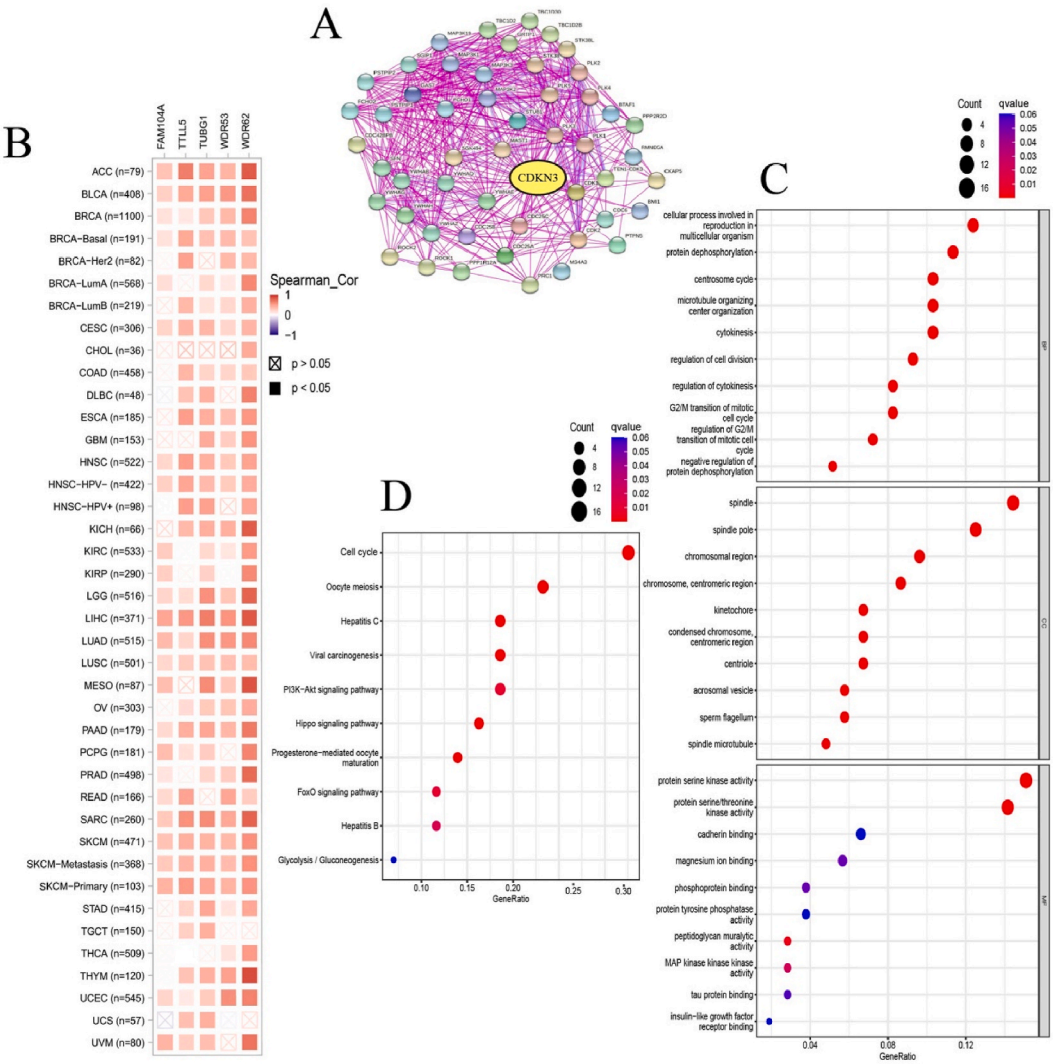

Fig. 6. Gene enrichment analysis of *CDKN3*. **(A)** 50 *CDKN3* binding protein interactions downloaded from the STRING website. **(B)** The corresponding heatmap data also showed a positive correlation between *CDKN3* and the above 5 genes in the most detailed cancer types which were downloaded from TIMER 2.0. **(C)** The enrichment analysis of Gene Ontology (GO) and **(D)** Kyoto encyclopedia of genes and genomes (KEGG).

4. Discussion

CDKN3 is a member of the dual-specific protein phosphatase family. It is not only a dephosphorylates cyclin dependent kinase, but also a key negative regulator of the cell cycle process, reducing the sensitivity of *p21* to promote cell proliferation and DNA repair. Due to the heterogeneity of tumors, the expression and function of a gene may be different in different tumors [107]. *CDKN3* has a bidirectional effect of promoting and inhibiting cell cycle phases, and its dysregulation or mutation is associated with several tumors. *CDKN3* can play a role in promoting tumors. Silencing the expression of *CDKN3* can reduce the sensitivity of hepatocellular carcinoma cells to Adriamycin [17]. However, it is not clear through what specific mechanism. In recent years, there have been a large number of *CDKN3* studies, and we have summarized and compared the currently available *CDKN3* and tumor studies. We found that the overexpression of *CDKN3* is related to the development and poor prognosis of some tumors. The expression of *CDKN3* is either up or down in different types of tumors. We systematically reviewed the expression and role of *CDKN3* in 18 different tumors, including 68 experimental studies and bioinformatics studies. And then we demonstrate in detail the pan-cancer effect of *CDKN3*, which depends on public databases such as TCGA and GETx. Finally, the role of *CDKN3* in promoting tumors was determined.

Bioinformatics analysis provides a faster and more accurate way to target gene effects. Through pan-cancer analysis, we revealed the fact that the expression of *CDKN3* in 30 kinds of tumors. Compared with the expression of *CDKN3* in normal or paracancerous tissues, the difference was statistically significant. However, the expression of *CDKN3* is significantly lower in LAML and TGCT. The unity of the results of our literature review and this result makes the conclusion of the article more reliable. However, there is a significant difference in the intensity of expression in all kinds of tumors, which indicates that its role in tumorigenesis and

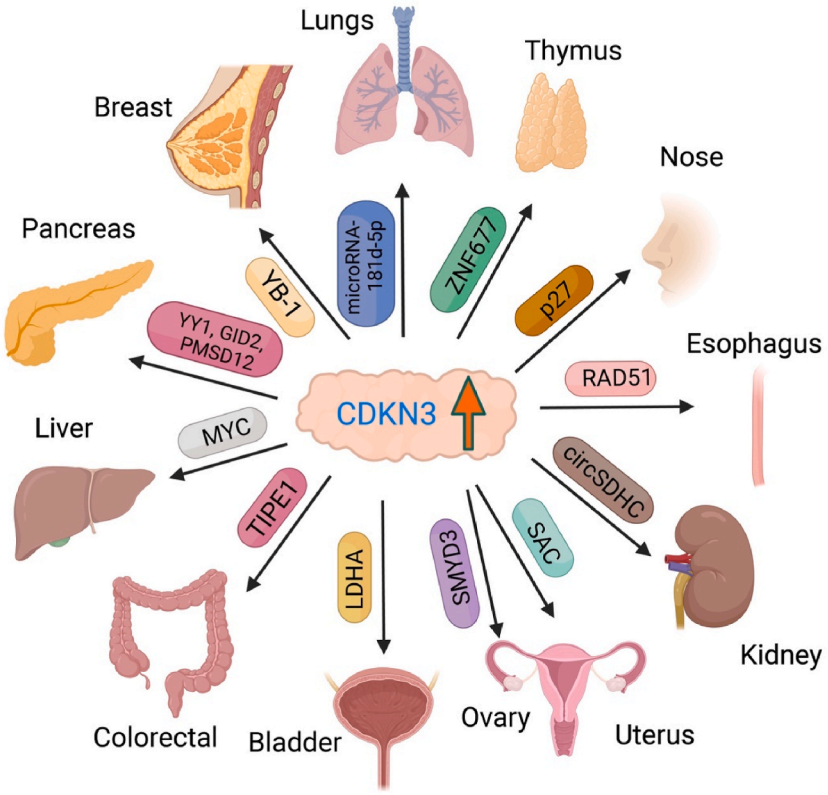

Fig. 7. *CDKN3*-dependent mechanisms in cancer promotion. Created with BioRender.com.

development may vary according to the tumor background. Even though it was shown overall that a high CDKN3 expression tends to play a role in promoting tumor progression. In addition, there were slight differences in the results of our literature review and pan-cancer analysis. In the literature review, chronic myelogenous leukemia is the only tumor in which *CDKN3* overexpression plays a role in tumor suppression. Therefore, larger sample size studies are needed to confirm the expression of *CDKN3* in these three types of tumors. From the further analysis of the survival in different cancer patients, we concluded that the overexpression of *CDKN3* led to a poor prognosis of ACC, KIRC, KIRP, LGG, LUAD, LUSC, PAAD, UVM, ESCA, LIHC, PRAD, SARC, and STAD. This result is highly consistent with the result of our literature review. We also analyzed the diagnostic value of *CDKN3* in the above tumors, and *CDKN3* showed acceptable diagnostic performance. However, at present, there are few studies in this area, and our research suggests that this may be a good direction. The specific mechanisms of *CDKN3* in tumors have been extensively studied. *CDKN3* acts in combination with several genes in the process of promoting tumor development (Fig. 7).

Gene mutation refers to a structural change in the composition or order of base pairs of a gene. Common types of mutations include silent mutations, missense mutations, insertion mutations, deletion mutations, and so on. Traditionally, it is believed that abnormal cell proliferation controlled by mutation is the core cause of tumorigenesis before the tumor microenvironment (TME) is not paid attention to Ref. [108]. Nowadays, targeted therapy and immunotherapy are rapidly becoming effective treatment options for various tumors [109,110]. We observed the genetic alteration status of *CDKN3* and found that the genetic alteration of LUAD, STAD, SARC, PCPG, and ESCA with "Amplification" is the main type. The CNA "Mutation" type is the main type for UCEC, TGCT, KIRC, and BLCA cases. Bin Yang et al. found that *CDKN3* was amplified by breakage-fusion-bridge cycles in lung adenocarcinoma through high-throughput sequencing, which provided experimental verification for our analysis results [111].

TME, referring to the cellular environment of the tumor, is complex and continuously evolving. TME includes various cells such as CAFs, T cells B cells, etc. Activated CAFs play an important role in the occurrence and development of tumors, including promoting tumor growth, invasion, and metastasis. And it has a great influence on extracellular matrix remodeling and even chemoresistance [112]. CAFs in the tumor microenvironment matrix regulate the function of many kinds of tumor-infiltrating immune cells [113,114]. In this study, we found that CAFs were positively correlated with ESCA, KICH, KIRC, KIRP, and THCA. It is suggested that among the five kinds of tumors, *CDKN3* may regulate TME through CAFS and play a role in promoting tumors, which may be one of the mechanisms. Tumor-infiltrating immune cells are one of the important components of the TME. It is closely related to the occurrence, development, and metastasis of tumors [115,116]. TFH is the most important helper cell of the B cell. Through Immune infiltration analysis, we found that *CDKN3* can promote the development of BRCA, GBM, KIRP, LIHC, STAD, THCA, THYM, and UVM by influencing TFH. Tregs are significantly increased in some tumors. *CDKN3* can promote the development of KIRC, LIHC, and THCA by

influencing Tregs. Therefore, the immune-related mechanisms of *CDKN3* in promoting tumor development deserve further investigation.

The unrestricted proliferation of tumor cells is a landmark feature of the tumor, which is closely related to the cell cycle [117]. The information on *CDKN3* binding components and *CDKN3* expression-related genes in all tumors was integrated. And then We performed a series of enrichment analyses, which determined the potential impact of the "cell cycle" and "mitosis" in cancer etiology and pathogenesis. *CDKN3* can regulate the transformation of cells from the G1 to S phase. This is consistent with the findings of previous studies [58]. Moreover, the phosphorylation activity of *CDKN3* is necessary to mediate apoptosis and carcinogenesis. As we mentioned earlier, *CDKN3* has a bidirectional regulatory effect on the cell cycle, which may be the reason *CDKN3* promotes and suppresses cancer, and it may also lead to its high or low expression in different types of tumors. *TTLL5*, *WDR40*, and *WDR62* are driving genes of some tumors [118–120].

CDKN3 is closely associated with the development of drug resistance in a variety of tumor types and may be an important target in future tumor therapy [55,57]. Bioinformatics relies on experimental science to generate raw data for analysis. They can make false predictions that make no sense when placed in a biological context. Therefore, our study incorporated as many reviews of *CDKN3* research as possible. A large number of bioinformatics analysis revealed the value of some tumors in *CDKN3*, but these often lack the verification of experimental and clinical studies. So even if *CDKN3* has been proven to be a good target, it is still difficult to use in clinical practice. Scientific research aims to ultimately serve clinical practice. Laboratory studies are usually conducted in a controlled environment, whereas clinical treatments need to take into account more variables, such as individual differences, complications, etc. We conducted a pan-cancer analysis and confirmed that *CDKN3* is of great value in tumors, but further experimental and clinical studies are needed. We have revealed part of the mechanism, which provides a direction for further research on the value of *CDKN3* in promoting human tumors. It is necessary to understand the role of *CDKN3* in tumorigenesis from the perspective of real data. Our study revealed the fact that the high expression of *CDKN3* plays a tumor-promoting role, but more in-depth evidence is needed to determine whether it plays a greater value.

5. Conclusion

CDKN3 is highly expressed in most tumor tissues and has a statistical correlation with survival prognosis. It has extensive tumor-promoting effects that may be related to mechanisms such as immune infiltration.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Data availability statement

All data included in this paper is publicly available, there is no restriction on availability. The datasets used and/or analyzed during the current study are available from the TCGA (https://portal.gdc.cancer.gov/) and GTEx (https://www.genome.gov/Funded-Programs-Projects/Genotype-Tissue-Expression-Project). Our study conformed to the publication guidelines provided by TCGA and GTEx. The original manuscript contained is included in the article/Supplementary Materials. Further inquiries can be acquired directly from the corresponding author.

CRediT authorship contribution statement

Chuanlong Zhang: Writing – original draft, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Qian Shen:** Software, Resources, Formal analysis, Data curation. **Mengqi Gao:** Writing – original draft, Software, Formal analysis, Data curation, Conceptualization. **Junchen Li:** Writing – review & editing, Methodology, Formal analysis. **Bo Pang:** Writing – review & editing, Validation, Project administration, Investigation, Funding acquisition, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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